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**UNITED STATES DISTRICT COURT**
**CENTRAL DISTRICT OF ILLINOIS**
**PEORIA DIVISION**

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| **LATOYA S. THOMPSON,**<br><br>**Plaintiff,**<br><br>**v.**<br><br>**BAYER HEALTHCARE PHARMACEUTICALS INC., BAYER PHARMA AG, and BAYER OY,**<br><br>**Defendants.** | **Case No. 1:15-cv-01117-JES-JEH** |

**DEFENDANTS' SUGGESTIONS IN OPPOSITION TO PLAINTIFF'S MOTION TO EXCLUDE OPINIONS OF REGULATORY EXPERTS DENA R. HIXON, M.D. AND DAVID W. FEIGAL JR., M.D.**

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## INTRODUCTION

Unable to attack the qualifications of Bayer's regulatory experts — Drs. Hixon and Feigal combined have dozens of years of relevant experience at the Food and Drug Administration ("FDA") — Plaintiff instead offers scattered criticisms that are unsupported by law or reason. Some arguments are plainly absurd: Plaintiff claims that the experts should be excluded for not reviewing hundreds of thousands of pages of irrelevant documents or because they cannot recall from rote memory the most minute details of studies they cite. Others are grossly misguided, including Plaintiff's assertion that experts must evaluate medical literature despite that literature's inability to offer insight on relevant issues (the Friedman articles), and her insistence that all experts must engage in the so-called Bradford-Hill causation assessment, regardless of the FDA's own standards. Plaintiff also argues against facts and reason. She alleges that Drs. Hixon and Feigal will present FDA "state of mind" testimony but is unable to identify any such testimony in their reports or depositions. She complains that Bayer will present duplicative testimony from both Drs. Hixon and Feigal, despite numerous assurances to the contrary. Finally, she asserts that Dr. Hixon's testimony in this case should be severely constrained based on findings in a separate case involving different issues. These nitpicking criticisms come nowhere close to justifying the sweeping exclusion Plaintiff seeks.[1]

## FACTUAL BACKGROUND

Dr. Dena Hixon is a licensed physician with nearly 13 years of experience as a Medical Officer at the FDA, including work in the Office of New Drugs, Division of Reproductive and

[1] Plaintiff's counsel has filed similar motions in multiple other cases; while the motions are still pending in several cases, they were denied in three cases. *See Hoover v. Bayer Healthcare Pharms.*, No. 3:14-cv-05090-SRB (W.D. Mo.) [Dec. 9, 2016 Order, ECF No. 117]; *Miller v. Bayer Healthcare Pharms.*, No. 4:14-cv-00652-SRB (W.D. Mo.) [Dec. 12, 2016 Order, ECF No. 111]; *Sellers v. Bayer Healthcare Pharms.*, No. 4:14-cv-00954-SRB (W.D. Mo.) [Dec. 12, 2016 Order, ECF No. 105].

Urologic Drug Products. Pl. Br. Ex. A, Hixon Report 1. In this role, Dr. Hixon repeatedly reviewed Investigational New Drug ("IND") applications, New Drug Applications ("NDA"), postmarketing labeling proposals, safety reports, and supplemental applications for new drug uses or changes in drug labeling. *Id.* Faced with this experience, Plaintiff is forced to concede Dr. Hixon's ample basis for offering her opinions: "She certainly possesses the regulatory qualifications to do so . . . ." Pl. Br. 10.

Dr. David Feigal is a licensed physician with 12 years of experience in various positions at the FDA, including 5 years at the FDA's Center for Drug Evaluation and Research ("CDER") in Director- and Acting Director-level positions. Ex. 1, Feigal Report 1–2. His responsibilities similarly included review and approval of product labeling, evaluating updated safety warnings, and assessing and providing initial approval for new medications. *Id*. at 2. Plaintiff cannot and does not challenge his qualifications: at the FDA, he served several levels above Plaintiff's proffered regulatory expert. Ex. 2, Ross Dep. 40:2–9.

In this matter, both experts wrote lengthy reports systematically addressing Mirena's regulatory history, including Bayer's consideration of the potential risk of IIH with Mirena use. They describe Mirena's labeling and opine that Bayer acted reasonably with respect to its evaluation of IIH in light of the available scientific evidence and the population using Mirena, including the fact that women who receive Mirena are at an especially high risk for the development of IIH. The experts reports meticulously supported their reports with citations to the extensive regulatory record they reviewed in formulating their opinions.

## LEGAL STANDARD

Under Rule 702, *Daubert*, and its progeny, expert testimony must be (1) reliable, (2) relevant and able to assist the jury, and (3) proffered by a qualified expert. Fed. R. Evid. 702;

*Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579, 589–95 (1993); *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 147–52 (1999). Experts are "qualified" if they possess "knowledge, skill, experience, training, or education" regarding the topics of their testimony. Fed. R. Evid. 702. To be reliable, expert testimony must be based on "sufficient facts or data" and must be "the product of reliable principles and methods" that have been "reliably applied" to the particular "facts of the case." Fed. R. Evid. 702; *see also, e.g.*, *Smoot v. Mazda Motors of Am., Inc.*, 469 F.3d 675, 681 (7th Cir. 2006). The purpose of conducting a *Daubert* inquiry is "'to make certain that an expert . . . employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.'" *Clark v. Takata Corp.*, 192 F.3d 750, 756 (7th Cir. 1999) (quoting *Kumho Tire*, 526 U.S. at 152).

## ARGUMENT

In place of offering a coherent, global challenge to Bayer's regulatory experts, Plaintiff offers scattershot criticisms that justify neither exclusion nor limitations on the relevant testimony.

### I. Drs. Hixon and Feigal Offer Reliable Opinions Based on Sufficient Facts and Data

#### A. *Daubert* Does Not Require Experts to Review Hundreds of Thousands of Pages of Documents and Depositions

Plaintiff offers blustery indignation over Dr. Hixon's decision not to review each of the nearly one million pages produced from Mirena's IND/NDA. Pl. Br. 11 ("According to counsel's latest count, approximately 481,000 pages have been produced under the MIR_INDNDA_ label and another 326,796 under the MIR_INDNDA-R_ label. ***Yet, Hixon never reviewed the entire file. Not even close***." (emphasis added)). Under this proposed standard, no expert report could ever be issued. Even at the blistering pace of one page per minute, reviewing a relatively modest 807,000-page IND/NDA would take approximately 6.5

years, working 40 hours per week, 52 weeks per year. *Daubert* and Rule 702 are not so draconian. Instead, they require that expert opinions be grounded in "sufficient facts or data." Fed. R. Evid. 702(b).

In place of reviewing pages of data irrelevant to her opinions, Dr. Hixon used her extensive regulatory experience to appropriately identify and review the relevant information. Plaintiff neither challenges Dr. Hixon's qualifications to do so, *see, e.g.*, Pl. Br. 10 (conceding that Dr. Hixon "***certainly possesses the regulatory qualifications***" to "review the [IND and NDA] for Mirena" (emphasis added)), nor offers any evidence or authority demonstrating that Dr. Hixon chose to review the "wrong" data.

As Dr. Hixon explained when she was challenged on this point, she applied just the kind of focused review in this case that FDA reviewers employ:

> DR. HIXON: I mean, all the raw data is analyzed in the study reports and it's reviewed at FDA and the information is summarized by the disciplines that are relevant to each section of the NDA.
>
> . . . A team leader would look at the reviews of -- the summary reviews of each individual discipline and go into any sections of the NDA that they needed to look at in order to reach their conclusion.
>
> Likewise, with the kind of task that I had before me here, that same sort of thing was the relevant information that needed to be reviewed, not to dig out every animal study, every piece of raw data from anything, but to get the overall big picture and look at the sections that are relevant to the question at hand.

Pl. Br. Ex. C, Hixon Dep. 29:2–21. Dr. Hixon employed her regulatory expertise to determine which materials were *not* relevant to her inquiry, such as "hundreds of thousands of pages of chemistry, manufacturing, and controls information." *Id.* at 25:5–7. By employing the same approach to her expert work that an FDA team leader uses when evaluating a new medication for approval, Dr. Hixon exercised "the same level of intellectual rigor that characterizes the practice

of an expert in the relevant field." *Kumho Tire*, 526 U.S. at 152.[2]

The same reasoning also dooms Plaintiff's tag-along criticism of both Drs. Hixon and Feigal for not recalling which depositions they read in full, versus depositions from which they read "key sections." Pl. Br. 4–5, 14–15. There is no basis for arguing that an expert may be excluded for not reading every page of testimony, particularly in the absence of ***any*** showing that the expert failed to review anything material. *See* Fed. R. Evid. 702 (expert testimony must be based on "sufficient facts or data").

### B. *Daubert* Does Not Require Experts to Memorize Details from Studies Cited in Their Reports

Plaintiff further highlights the flimsiness of her *Daubert* challenge by criticizing Dr. Hixon for not committing to rote memory minute details from studies cited in her report. Pl. Br. 6 (criticizing Dr. Hixon for not recalling details such as "the number of participants in the studies" and "the response rates"). Plaintiff does not and cannot argue that Dr. Hixon failed to provide support for key opinions about IIH incidence rates and risk factors in her heavily-footnoted report, and she offers no authority for her argument that a failure to recall details from studies requires exclusion under *Daubert*.[3]

Memorization of minute details is not a metric for the reliability or helpfulness of an expert's opinion, nor should it be. Any "lapses in memory are traditionally challenged through

[2] There is some irony to this criticism, given that Plaintiff's own regulatory experts do not purport to have conducted such an extensive review — indeed, Dr. Fraunfelder spent a grand total of ten hours in reviewing materials and writing his report. Dr. Hixon reviewed not only all of the materials purportedly relied upon by Drs. Ross and Fraunfelder, but also more than 200 additional documents.

[3] In addition to being irrelevant, Plaintiff's criticism of Dr. Hixon's memory is inaccurate and unfair. Dr. Hixon recalled significant details about certain studies and engaged in extensive questioning with counsel on issues of study designs and findings. *See, e.g.*, Pl. Br. Ex. C, Hixon Dep. 80:13–82:21 (discussing the Durcan study). Counsel also repeatedly refused Dr. Hixon's request for copies of studies to refresh her recollection. *See id*. at 80:25–81:2, 87:19–88:3.

cross-examination and do not render [expert] opinion testimony unreliable." *Pension Comm. of Univ. of Montreal Pension Plan v. Banc of Am. Sec., LLC*, 716 F. Supp. 2d 220, 227 n.45 (S.D.N.Y. 2010).

**C. Dr. Hixon's Regulatory Role Includes Review of IIH Data and Risk Factors**

Plaintiff's criticism of Dr. Hixon's memory is embedded within a claim that she steps beyond her "regulatory role" when testifying as to IIH incidence rates and risk factors. Pl. Br. 6. This criticism demonstrates a fundamental misunderstanding of the regulatory expert's role. One of Dr. Hixon's major tasks in this litigation is to assess the adequacy of Mirena's IIH labeling. No expert can analyze the adequacy of Mirena's IIH labeling without developing some understanding of the disease, its incidence rate, and its relevant risk factors. Indeed, understanding the underlying epidemiology of the disease and related risk factors constitutes an essential aspect of evaluating whether a potential risk should appear in a medicine's label. *See* FDA, *Guidance for Industry: Good Pharmacovigilance Practices* (2005), *available at* http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf ("To provide further context for incidence rates or reporting rates, it is helpful to have an estimate of the background rate of occurrence for the event being evaluated in the general population or, ideally, in a subpopulation with characteristics similar to that of the exposed population (e.g., premenopausal women, diabetics)."). As Dr. Hixon explained in her deposition, FDA regulators consider this type of data throughout the regulatory process:

> I do have some expertise in those fields [epidemiology and pharmacokinetics] just by virtue of the kind of work I did at FDA that incorporated those kinds of data into the regulation process.

Pl. Br. Ex. C, Hixon Dep. 75:23–76:1.

By considering the same types of data that FDA regulators consider when making approval decisions, Dr. Hixon has approached her expert work with the same degree of intellectual rigor employed by experts in her field.

### D. *Daubert* Does Not Require Experts to Review a Particular Article When They Have Considered the Relevant Underlying Data

Plaintiff criticizes Drs. Hixon and Feigal for not citing a small number of review publications by Dr. Deborah Friedman that list levonorgestrel, the synthetic hormone used in Mirena, among other substances that may be "associated" with IIH. *See* Pl. Br. 7–8, 15. But it is meritless to claim that an expert opining on a potential relationship between a medication and an event must cite every article that makes even a passing reference to a potential *association* between the substance and the relevant condition. This conclusion is plain from the briefest review of Dr. Friedman's passing references to levonorgestrel. Dr. Friedman's articles — none of which reports original research — refer only to a potential "association" between levonorgestrel and IIH. The articles do not even discuss Mirena; instead, they cite literature about Norplant, a different contraceptive system, and one that Drs. Hixon and Feigal expressly considered. *Compare* Pl. Br. Exs. G, H, I, K (Friedman publications each citing Norplant information), *with* Pl. Br. Ex. A, Hixon Report 21–28 (discussing Norplant information), *and* Ex. 1, Feigal Report 25–29 (same).

Drs. Hixon and Feigal fully considered the available evidence concerning Norplant and explained that Norplant's potential risks are not automatically attributable to Mirena. As discussed in the Hixon and Feigal reports, Norplant was implanted into women's arms and circulated levonorgestrel throughout their bloodstreams. Mirena also contains levonorgestrel, but in a significantly lower dose, which is delivered directly to the uterus, rather than circulating systemically. These differences affect the medications' risk profiles, and as Drs. Hixon and

Feigal explain, evidence regarding Norplant and IIH is not relevant for assessing whether there is a causal relationship between Mirena and IIH. Pl. Br. Ex. A, Hixon Report 21–28; Ex. 1, Feigal Report 25–29. The reliability of their opinions is in no way undermined because they did not cite to an article that merely referenced the very potential association they fully considered.

### E. *Daubert* Does Not Require Defense Regulatory Experts to Apply the Bradford-Hill Causation Analysis

Plaintiff contends that Drs. Hixon and Feigal should be excluded for their decision not to engage in a "proper" analysis of the so-called Bradford-Hill causation factors.[4] Plaintiff's criticism is inapposite for two reasons.

First, Plaintiff has not demonstrated that the Bradford-Hill criteria are applicable to this case. As Bradford-Hill himself explained, the framework applies only after an "association between two variables" is "perfectly clear-cut and beyond what we would care to attribute to the play of chance." *Dunn v. Sandoz Pharms. Corp.*, 275 F. Supp. 2d 672, 678 (M.D.N.C. 2003) (quoting Bradford Hill, *The Environment and Disease: Association or Causation*, 58 Proc. Royal Soc'y Med. 295, 295–300 (1965)); Ex. 1, Feigal Report 48. After a rigorous assessment of the evidence, Drs. Hixon and Feigal determined that there was not a "perfectly clear-cut" association between Mirena and IIH, and thus made the reasoned decision not to engage in a Bradford-Hill assessment. *See* Ex. 1, Feigal Report 24–50; Pl. Br. Ex. A, Hixon Report 21–36. Plaintiff may disagree with their conclusions, but that disagreement does not give rise to any legitimate

[4] The Bradford-Hill factors are one set of guidelines, comprising nine criteria, which epidemiologists may, under certain circumstances, consider when assessing whether a causal relationship exists between a putative cause and effect.

*Daubert* challenge.[5] *Daubert*, 509 U.S. at 595 (the court focuses on experts' principles and methodology, "not on the conclusions that they generate").

Second, Plaintiff makes no showing that an expert must engage in a Bradford-Hill analysis to support a causation opinion, let alone a regulatory opinion. *See* Pl. Br. Ex. C, Hixon Dep. 75:1–2 ("My role is purely as a regulatory expert, *not as a causation expert* . . . ." (emphasis added)); *In re Celexa & Lexapro Prod. Liab. Litig.*, 927 F. Supp. 2d 758, 766 (E.D. Mo. 2013) ("Although the Bradford Hill criteria may be a tool for determining whether an epidemiological study establishes causation, ***it is by no means required*** . . . ." (emphasis added) (citation omitted)). Tasked with assessing the adequacy of Mirena's labeling, both experts turn to the FDA's *Guidance for Industry: Good Pharmacovigilance Practices*, which lists seven factors to consider when assessing the relationship between a medication and an adverse outcome. Pl. Br. Ex. A, Hixon Report 29–30; Ex. 1, Feigal Report 31–32. Drs. Hixon and Feigal properly applied these standards, and Plaintiff does not argue otherwise (or even mention these standards).

## II. Drs. Hixon and Feigal Do Not Offer "State of Mind" Testimony

Plaintiff claims that Drs. Hixon and Feigal both "*attempt*" to offer opinions that "*suggest*" that the FDA would not approve an IIH warning on the Mirena label. Pl. Br. 16 (emphasis added). This accusation is simply not correct, as demonstrated by Plaintiff's inability to cite support for this claim in either expert's report or deposition. In fact, neither Dr. Hixon nor Dr. Feigal offer any opinion regarding whether the FDA would approve an IIH warning.

[5] Dr. Feigal elected to address Bradford-Hill as applied by one of Plaintiff's experts, who has since been withdrawn. Ex. 1, Feigal Report 48–50.

## III. Plaintiff Is Not "Unfairly Prejudiced" by Dr. Hixon's Testimony

Plaintiff makes the footnote argument that Dr. Hixon's testimony should be limited due to certain restrictions she faced in the Mirena uterine perforation MDL.[6] In that litigation, Dr. Hixon was unable to disclose due to confidentiality concerns a few specific internal FDA conversations that directly related to the risk of perforation. Believing that the plaintiffs could be "unfairly prejudiced" because Dr. Hixon had "participated directly in some of the events at issue but [could not] discuss them," the MDL court carved out limited portions of her testimony. Pl. Br. 9–10 n.2.

Plaintiff has offered no justification for the same ruling here on the distinct IIH issue. Dr. Hixon's report and testimony make clear that she does not rely on "insider information" to support her positions. Each of her opinions is supported by either publically-available documents or materials produced in this litigation. At no point during her IIH deposition did Dr. Hixon refuse to answer counsel's questions, and Plaintiff has taken no steps to develop a record of prejudice resulting from Dr. Hixon's testimony. In short, nothing in the record suggests that Dr. Hixon "could not fully disclose the bases of her opinions." *Id.* Plaintiff should not be permitted to limit Dr. Hixon's testimony by piggybacking off an unrelated finding, made by another court in another case, involving testimonial limitations that are not at issue here.

## IV. Bayer Will Not Present Duplicative Regulatory Testimony

Plaintiff need not be concerned that Bayer will present duplicative regulatory testimony in this case. Trial is months away, and Bayer has made it abundantly clear to Plaintiff that at

[6] The plaintiffs in the Mirena MDL perforation litigation alleged that properly-inserted Mirenas spontaneously perforated through the uterus and into the abdominal cavity. Bayer secured summary judgment in the MDL after the plaintiffs' general causation experts were excluded under *Daubert*.

trial it will not offer improperly cumulative testimony. *See* Pl. Br. Ex. E ("[W]e do not intend to violate the court rules on presenting cumulative testimony at trial."). Bayer will not call both Dr. Hixon and Dr. Feigal, and Plaintiff offers no authority suggesting that now, at the *Daubert* stage, Bayer is obligated to select its trial witnesses. *See In re Mirena IUD Prod. Liab. Litig.*, No. 13-CV-6586 (CS), 2016 WL 890251, at *42 (S.D.N.Y. Mar. 8, 2016) (denying as moot plaintiffs' "motion with respect to the cumulative nature of Dr. Feigal's testimony" because Bayer confirmed that it would not be presenting cumulative testimony at any given trial).

## CONCLUSION

For the foregoing reasons, Plaintiff's motion should be denied.

Dated: March 29, 2017

Respectfully Submitted,

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**CERTIFICATE OF SERVICE**

I hereby certify that I electronically filed on March 29, 2017, the foregoing with the Clerk of the Court using the CM/ECF system which will send notification of such filing to the following:

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